format. Support for the amendment is found, for example, in pages 58-69 as originally filed.

No new matter is added in any of the above amendment and the Examiner is respectfully requested to enter the amendments and reconsider the application.

The Response

1. Objection to specification

The Examiner objected to the specification in that the disclosures in pages 58-69 were cited in a claim format. The Applicants avoid this objection by amending the specification so that it is not in the claim format. Since no portion of the amended specification is in the claim format, Applicants respectfully request the Examiner to withdraw this objection.

2. 35 U.S.C. § 102(e)

The Examiner rejects Claims 1 and 2 under 35 U.S.C. § 102(e) as being anticipated by Desnick, *et al.* (U.S. Pat. No. 5,40,650; hereafter the "'650 patent"). Applicants respectively traverse this rejection because (1) the '650 patent does not qualify as a § 102(e) reference, and (2) the '650 patent does not teach every element of the claims.

MPEP 2131 states:

> "TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM
> 'A claim is anticipated only if each and every element as et forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 9 USPQ2d 1913 (Fed. Cir. 1989)."

The '650 patent was filed on November 30, 1992, and issued on March 28, 1995. The present application claims priority to U.S. Patent Application Serial No. 07/160,766, filed February 26, 1988, and thus is deemed to be constructively reduced to practice by February 26, 1988. Since the '650 patent was filed subsequent to the date the Claims 1 and 2 are constructively reduced to practice, **the '650 patent does not qualify as a § 102(e) reference** [illegible] Claims of this present application

"Alternative eukaryotic expression systems which may be used to express the α-Gal A enzymes are . . . plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing the α-Gal A coding sequence.

. . .

In cases where plant expression vectors are used, the expression of the α-Gal A coding sequence may be driven by any of a number of promoters. For example, viral promoters such as the 35S RNA and 19S RNA promoters of CaMV (Brisson et al., 1984, Nature 310:511-514), or the coat protein promoter of TMV (Takamatsu et al., 1987, EMBO J. 6:307-311) may be used; alternatively, plant promoters such as the small subunit of RUBISCO (Coruzzi et al., 1984, EMBO J. 3:1671-1680; Broglie et al., 1984, Science 224:838-843); or heat shock promoters, e.g., soybean hsp17.5-E or hsp17.3-B (Gurley et al., 1986, Mol. Cell. Biol. 6:559-565) may be used. These constructs can be introduced into plant cells using Ti plasmids, Ri plasmids, plant virus vectors; direct DNA transformation; microinjection, electroporation, etc. For reviews of such techniques see, for example, Weissbach & Weissbach, 1988, Methods for Plant Molecular Biology, Academic Press, NY, Section VIII, pp. 421-463; and Grierson & Corey, 1988, Plant Molecular Biology, 2d Ed., Blackie, London, Ch. 7-9." (col. 16, lines 39-50; col. 17, lines 12-32)

The '650 patent merely teaches the production of human galactosidase A in mammalian cells using a chromosomally integarted nucleotide sesequence encoding human galactosidase A. The '650 patent does not provide any further teaching or any working example regarding a recombinant expression construct comprising a nucleotide sequence encoding a protein of choice and a promoter that regulates the expression of the nucleotide sequence in a plant cell. The '650 patent does not enable any a recombinant expression construct would in fact be able to express a lysosomal enzyme or any other protein of choice in a plant cell. The '650 patent does not enable the expression of any lysosomal enzyme or any other protein of choice in a plant cell would produce a properly folded and processed lysosomal enzyme or any other protein of choice. Mammalian cells are biologically significantly different from plant cells. A promoter that can express a nucleotide sequence in a mammalian cell cannot necessarily express that nucleotide sequence in a plant cell, and vice versa. The '650 patent does not provide sufficient teaching to enable one of ordinary skill in the art to make or use a recombinant expression construct comprising a nucleotide sequence

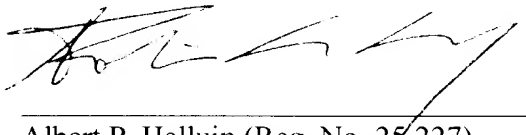
and 2, therefore the '650 patent does not teach every element of the claims. Hence, the '650 patent does not anticipate Claims 1 and 2.

For the reason stated above, the 35 U.S.C. § 102(e) rejection of Claims 1 and 2 over the '650 patent should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe the application is in good and proper condition for allowance. Early notification of allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109. A telephone conference is especially requested if the Examiner intends to maintain the present rejections.

Respectfully submitted,



Date: September 20, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Please amend the following text in page 58, line 12 to page 69, line 4 as follows:

"[1. A] The present invention provides for a method for producing a protein of choice comprising a lysosomal enzyme which is enzymatically active, comprising:[

]recovering the lysosomal enzyme from (i) a transgenic plant cell or (ii) a cell, tissue or organ of a transgenic plant, which transgenic plant cell or plant is transformed or transfected with a recombinant expression construct comprising a nucleotide sequence encoding the lysosomal enzyme and a promoter that regulates expression of the nucleotide sequence so that the lysosomal enzyme is expressed by the transgenic plant cell or plant.[

2. The method according to claim 1, in which the] The promoter [is] can be an inducible promoter.[

3. The method according to claim 2, in which the] The inducible promoter [is] can be induced by mechanical gene activation.[

4.] The method [according to claim 2, which is] can be carried out with the transgenic plant and additionally comprises a step of inducing the inducible promoter before or after the transgenic plant is harvested, which inducing step is carried out before recovering the lysosomal enzyme from the cell, tissue or organ of the transgenic plant.[

5. The method according to claim 1, in which the] The lysosomal enzyme [is] can be a modified lysosomal enzyme which is enzymatically active and comprises: [

](b) the human or animal lysosomal enzyme or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the human or animal lysosomal enzyme or (a); or[

](c) the human or animal lysosomal enzyme or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

6. The method according to claim 5, in which the] The modified lysosomal enzyme [comprises] can comprise a signal peptide or detectable marker peptide at the amino or carboxyl terminal of the modified lysosomal enzyme. [

7. The method according to claim 6, in which the] The modified lysosomal enzyme [is] can be recovered from (i) the transgenic plant cell or (ii) the cell, tissue or organ of the transgenic plant by reacting with an antibody that binds the detectable marker peptide. [

8. The method according to claim 7, in which the] The antibody [is] can be a monoclonal antibody. [

9. The method according to claim 5, in which the] The modified lysosomal enzyme [comprises] can comprise : [

](a) an enzymatically-active fragment of an *a*.-N-acetylgalactosaminidise, acid lipase, *a*-galactosidase, glucocerebrosidase, *a*.-L-iduronidase, iduronak sulfatase, *a*-mannosidase or sialidase; [

](b) the *a*-N-acetylgalactosaminidase, acid lipase, *a*-galactosidase, glucocerebrosidase, *a*-L-iduronidase, iduronate sulfatase, *a*-mannosidase, sialidase or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the *a*-N-acetylgalactosaminidase, acid lipase, *a*-galactosidase, glucocerebrosidase, *a*-L-

](c) the *a*-N-acetylgalactosaminidase, acid lipase, *a*-galactosidase, glucocerebrosidase, *a*-L-iduronidase, iduronate sulfatase, *a*-mannosidase, sialidase or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

10. The method according to claim 9, in which the] The modified lysosomal enzyme [comprises] can comprise : [

](a) an enzymatically-active fragment of a human glucocerebrosidase or human α-L-iduronidase enzyme; [

](b) the human glucocerebrosidase, human α-L-iduronidase or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the human glucocerebrosidase, human α-L-iduronidase or (a); or [

](c) the human glucocerebrosidase, human α-L-iduronidase or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

11. The method according to claim 5, in which the] The modified lysosomal enzyme [is] can be a fusion protein comprising: [

](I) (a) the enzymatically-active fragment of the human or animal lysosomal enzyme, [

](b) the human or animal lysosomal enzyme, or [

](c) the human or animal lysosomal enzyme or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions, and [

](II) a cleavable linker fused to the amino or carboxyl terminus of (I); and the method comprises: [

](a) recovering the fusion protein from the transgenic plant cell, or the cell, tissue or organ of the transgenic plant; [

](b) treating the fusion protein with a substance that cleaves the cleavable linker so that (I)is separated from the cleavable linker and any sequence attached thereto; and [

](c) recovering the separated (I). [

12. The method according to claim 1, in which the] The transgenic plant [is] can be a transgenic tobacco plant. [

13. The method according to claim 1, in which the] The lysosomal enzyme [is] can be a human or animal lysosomal enzyme. [

14. The method according to claim 13, in which the] The lysosomal enzyme [is] can be an α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase or sialidese. [

15. The method according to claim 14, in which the] The lysosomal enzyme [is] can be a human glucocerebrosidase or human α-L-iduronidase. [

16. The method according to claim 1, in which the] The organ [is] can be a leaf, stem, root, flower, fruit or seed.

[17. A] The present invention provides for a recombinant expression construct comprising a nucleotide sequence encoding a protein of choice comprising a lysosomal enzyme and a promoter that regulates the expression of the nucleotide sequence in a plant cell. [

19. The recombinant expression construct of claim 18, in which the] The inducible promoter [is] can be induced by mechanical gene activation. [

20. The recombinant expression construct of claim 17, in which the] The lysosomal enzyme [is] can be a modified lysosomal enzyme which is enzymatically active and comprises: [

](a) an enzymatically-active fragment of a human or animal lysosomal enzyme; [

](b) the human or animal lysosomal enzyme or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the human or animal lysosomal enzyme or (a); or [

](c) the human or animal lysosomal enzyme or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

21. The recombinant expression construct of claim 20, in which the] The modified lysosomal enzyme [comprises] can comprise a signal peptide or detectable marker peptide at the amino or carboxyl terminal of the modified lysosomal enzyme. [

22. The recombinant expression construct of claim 21, in which the] The detectable marker peptide 15 [comprises] can comprise SEQ ID NO: 10. [

23. The recombinant expression construct of claim 20, in which the] The modified lysosomal enzyme [comprises:

] can comprise (a) an enzymatically-active fragment of an α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-

](b) the α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase, sialidase or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase, sialidase or (a); or [

](c) the α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase, sialidase or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

24. The recombinant expression construct of claim 23, in which the] The modified lysosomal enzyme [comprises:

] can comprise (a) an enzymatically-active fragment of a human glucocerebrosidase or human α-L-iduronidase enzyme; [

](b) the human glucocerebrosidase or human α-L-iduronidase or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the human glucocerebrosidase, human α-L-iduronidase or (a); or [

](c) the human glucocerebrosidase, human α-L-iduronidase or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

25. The expression construct of claim 20, in which the] The modified lysosomal enzyme [is] can be a fusion protein comprising [

] can comprise: (I) (a) the enzymatically-active fragment of the human or animal lysosomal enzyme, [

](c) the human or animal lysosomal enzyme or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions, and [

](II) a cleavable linker fused to the amino or carboxyl terminus of (I). [

26. The recombinant expression construct of claim 17, in which the] The lysosomal enzyme [is] can be a human or animal lysosomal enzyme. [

27. The recombinant expression construct of claim 25, in which the] The lysosomal enzyme [is] can be an α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase or sialidase. [

28. The recombinant expression construct of claim 27, in which the] The lysosomal enzyme [is] can be a human glucocerebrosidase or human α-L-iduronidase. [

29. A] The present invention provides for a plant transformation vector comprising any of the recombinant expression construct [of claim 17, 18, 20, 21, 24, 25, or 28] recited above . [

30. A] The present invention provides for a plant which is transformed or transfected with any of the recombinant expression construct [of claim 17, 18, 20, 21, 24, 25, or 28] recited above . [

31. A] The present invention provides for a plant cell, tissue or organ which is transformed or transfected with any of the recombinant expression construct [of claim 17, 18, 20, 21, 24, 25, or 28] recited above . [

32. A] The present invention provides for a plant transfection vector comprising any of the recombinant expression construct [of claim 17, 18, 20, 21, 24, 25, or 28] recited

33. A] The present invention provides for a plasmid comprising any of the recombinant expression construct [of claim 17, 18, 20, 21, 24, 25, or 28] recited above . [

34. A] The present invention provides for a transgenic plant or plant cell capable of producing a lysosomal enzyme which is enzymatically active, which transgenic plant or plant cell is transformed or transfected with a recombinant expression construct comprising a nucleotide sequence encoding a lysosomal enzyme and a promoter that regulates expression of the nucleotide sequence in the transgenic plant or plant cell. [

35. The transgenic plant or plant cell of claim 34, in which the] The promoter is an inducible promoter. [

36. The transgenic plant or plant cell of claim 35, in which the] The inducible promoter is induced by mechanical gene activation. [

37. The transgenic plant or plant cell of claim 36, in which the] The inducible promoter comprises SEQ ID NO: 5. [

38. The transgenic plant or plant cell of claim 34, in which the] The lysosomal enzyme which is a modified lysosomal enzyme which is enzymatically active and which comprises: [

](a) an enzymatically-active fragment of a human or animal lysosomal enzyme; [

](b) the human or animal lysosomal enzyme or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the human or animal lysosomal enzyme or (a); or [

](c) the human or animal lysosomal enzyme or (a) having one or more naturally-

39. The transgenic plant or plant cell of claim 38, in which the] The modified lysosomal enzyme comprises a signal peptide or detectable marker peptide at the amino or carboxyl terminal of the modified lysosomal enzyme. [

40. The transgenic plant or plant cell of claim 39, in which the] The detectable marker peptide comprises SEQ ID NO: 10. [

41. The transgenic plant or plant cell of claim 38, in which the] The modified lysosomal enzyme comprises: [

](a) an enzyrnatically-active fragment of an α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase or sialidase; [

](b) the α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase, sialidase or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, amannosidase, sialidase or (a); or [

](c) the α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase, sialidase or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

42. The transgenic plant or plant cell of claim 41, in which the] The modified lysosomal enzyme comprises: [

](a) an enzymatically-active fragment of a human glucocerebrosidase or human α-L-iduronidase enzyme; [

](b) the human glucocerebrosidase, human α-L-iduronidase or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the human glucocerebrosidase, human α-L-iduronidase or (a); or [

](c) the human glucocerebrosidase, human *a*-L-iduronidase or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

43. The transgenic plant or plant cell of claim 38, in which the] The modified lysosomal enzyme is a fusion protein comprising: [

](I) (a) the enzymatically-active fragment of the human or animal lysosomal enzyme, [

](b) the human or animal lysosomal enzyme, or [

](c) the human or animal lysosomal enzyme or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions, and [

](II) a cleavable linker fused to the amino or carboxyl terminus of (I). [

44. The transgenic plant or plant cell of claim 34, in which the] The transgenic plant or plant cell is a transgenic tobacco plant or tobacco cell. [

45. The transgenic plant or plant cell of claim 34, in which the] The lysosomal enzyme is a human or animal lysosomal enzyme. [

46. The transgenic plant or plant cell of claim 45, in which the] The lysosomal enzyme is an *a*-N-acetylgalactosaminidase, acid lipase, *a*-galactosidase, glucocerebrosidase, *a*-L-iduronidase, iduronate sulfatase, *a*-mannosidase or sialidase. [

48. A] The present invention provides for a leaf, stem, root, flower or seed of any of the transgenic plant [of claim 34, 35, 38, 39, 42, 44, 45, or 47] recited above . [

49. A] The present invention provides for a seed of plant line Nicotiana sp., which seed has the ATCC Accession No. -------, deposited July 25, 2000. [

50. A] The present invention provides for a plant grown from the seed [of claim 49] recited above . [

51. A] The present invention provides for a lysosomal enzyme which is enzymatically active and is produced according to a process comprising: [

]recovering the lysosomal enzyme from (i) a transgenic plant cell or (ii) a cell, tissue or organ of a transgenic plant which transgenic plant cell or plant is transformed or transfected with a recombinant expression construct comprising a nucleotide sequence encoding the lysosomal enzyme and a promoter that regulates expression of the nucleotide sequence so that the lysosomal enzyme is expressed by the transgenic plant cell or plant. [

52. The lysosomal enzyme of claim 59, in which the] The promoter [is] can be an inducible promoter.[

53. The lysosomal enzyme of claim 52, which] The process is carried out with the transgenic plant and additionally [comprises] can comprise a step of inducing the inducible promoter before or after the transgenic plant is harvested, which inducing step is carried out before recovering the lysosomal enzyme from the cell, tissue or organ of the transgenic plant. [

54. The lysosomal enzyme of claim 51, which is a] The modified lysosomal enzyme

] can comprise: (a) an enzymatically active fragment of a human or animal lysosomal enzyme; [

](b) the human or animal lysosomal enzyme or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the human or animal lysosomal enzyme or (a); or[

](c) the human or animal lysosomal enzyme or (a) having one or more naturally-occurring amino acid, additions, deletions or substitutions. [

55. The lysosomal enzyme of claim 54, in which the] The modified lysosomal enzyme [comprises] can comprise a signal peptide or detectable marker peptide at the amino or carboxyl terminal of the modified lysosomal enzyme. [

56. The lysosomal enzyme of claim 54, in which the] The modified lysosomal enzyme [comprises:

] can comprise: (a) an enzymatically-active fragment of an α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase or sialidase; [

](b) the α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase, sialidase or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, amannosidase, sialidase or (a); or [

](c) the α-N-acetylgalactosaminidasd, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfazase, α-mannosidase, sialidase or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

57. The lysosomal enzyme of claim 56, in which the] The modified lysosomal enzyme comprises: [

](a) an enzymatically-active fragment of a human glucocerebrosidase or human α-L-iduronidase enzyme; [

](b) the human glucocerebrosidase, human α-L-iduronidase or (a) having one or more amino acid residues added to the amino or carboxyl terminus of the human glucocerebrosidase, human α-L-iduronidase or (a); or [

](c) the human glucocerebrosidase, human α-L-iduronidase or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions. [

58. The lysosomal enzyme of claim 54, in which the] The modified lysosomal enzyme [is] can be a fusion protein comprising: [

](I) (a) the enzymatically-active fragment of the human or animal lysosomal enzyme, [

](b) the human or animal lysosomal enzyme, or [

](c) the human or animal lysosomal enzyme or (a) having one or more naturally-occurring amino acid additions, deletions or substitutions, and [

](II) a cleavable linker fused to the amino or carboxyl terminus of (I). [

59. The lysosomal enzyme of claim 51, in which the] The transgenic plant [is] can be a transgenic tobacco plant. [

60. The lysosomal enzyme of claim 51, in which the] The lysosomal enzyme [is] can

61. The lysosomal enzyme of claim 60, in which the] The lysosomal enzyme [is] can be an α-N-acetylgalactosaminidase, acid lipase, α-galactosidase, glucocerebrosidase, α-L-iduronidase, iduronate sulfatase, α-mannosidase or sialidase. [

62. The lysosomal enzyme of claim 61, in which the] The lysosomal enzyme [is] can be a human glucocerebrosidase or human α-L-iduronidase. [

63. The lysosomal enzyme of claim 51, in which the] The organ [is] can be a leaf, stern, root, flower, fruit or seed."